Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Increased uptake and new therapies are needed to avert rising hepatitis C-related end stage liver disease in England: Modelling the predicted impact of treatment under different scenarios

Ross J. Harris[1], Brenda Thomas[2], Jade Griffiths[2], Annastella Costella[2], Ruth Chapman[3], Mary Ramsay[2], Daniela De Angelis[1,4], Helen E. Harris[2,*]

[1]*Statistics, Modelling and Bioinformatics Department, Centre for Infectious Disease Surveillance and Control, Public Health England, 61 Colindale Avenue, London NW9 5EQ, United Kingdom;* [2]*Immunisation, Hepatitis and Blood Safety Department, Centre for Infectious Disease Surveillance and Control, Public Health England, 61 Colindale Avenue, London NW9 5EQ, United Kingdom;* [3]*United BioSource Corporation, 26-28 Hammersmith Grove, London W6 7HA, United Kingdom;* [4]*MRC Biostatistics Unit, Cambridge Institute of Public Health, Forvie Site, Robinson Way, Cambridge Biomedical Campus, Cambridge CB2 0SR, United Kingdom*

Background & Aims: Hepatitis C (HCV) related disease in England is predicted to rise, and it is unclear whether treatment at current levels will be able to avert this. The aim of this study was to estimate the number of people with chronic HCV infection in England that are treated and assess the impact and costs of increasing treatment uptake.

Methods: Numbers treated were estimated using national data sources for pegylated interferon supplied, dispensed, or purchased from 2006 to 2011. A back-calculation approach was used to project disease burden over the next 30 years and determine outcomes under various scenarios of treatment uptake.

Results: 5000 patients were estimated to have been treated in 2011 and 28,000 in total from 2006 to 2011; approximately 3.1% and 17% respectively of estimated chronic infections. Without treatment, incident cases of decompensated cirrhosis and hepatocellular carcinoma were predicted to increase until 2035 and reach 2290 cases per year. Treatment at current levels should reduce incidence by 600 cases per year, with a peak around 2030. Large increases in treatment are needed to halt the rise; and with more effective treatment the best case scenario predicts incidence of around 500 cases in 2030, although treatment uptake must still be increased considerably to achieve this.

Conclusions: If the infected population is left untreated, the number of patients with severe HCV-related disease will continue to increase and represent a substantial future burden on healthcare resources. This can be mitigated by increasing treatment uptake, which will have the greatest impact if implemented quickly.

Keywords: Back-calculation; Disease burden; Hepatitis C; Liver disease; Modelling; Treatment.

Received 19 March 2013; received in revised form 28 February 2014; accepted 3 May 2014; available online 10 May 2014

* Corresponding author. Address: Immunisation, Hepatitis and Blood Safety Department, Centre for Infectious Disease Surveillance and Control, Public Health England, 61 Colindale Avenue, London NW9 5EQ, United Kingdom.

E-mail address: helen.harris@phe.org.uk (H.E. Harris).

Abbreviations: HCV, hepatitis C; NHS, National Health Service; NICE, National Institute for Health and Care Excellence (formally National Institute for Health and Clinical Excellence); HPAI, Hospital Pharmacy Audit Index; ESLD, end-stage liver disease; HCC, hepatocellular carcinoma; HES, Hospital episode statistics; SVR, sustained viral response; DAA, direct acting antiviral; QALY, quality adjusted life year; CrI, credible interval.

Introduction

The Health Protection Agency estimated that in 2005, 161,000 adults in England were chronically infected with hepatitis C (HCV) [1]. National data sources show that HCV-related liver disease is increasing, with predictions indicating that this trend will continue for at least the next 10 years [2,3]. This will place a substantial burden on healthcare services and result in a significant reduction in lifespan for many infected individuals.

Treating HCV infected patients presents a considerable challenge for the National Health Service (NHS) as many infections are undiagnosed [3] and treatment is not successful in every case [4–8]. A significant proportion of the infected population, including people who inject drugs and minority ethnic populations, are 'hard to reach' and service provision has been shown to vary geographically and not always be configured to allow easy access to these groups [9]. Despite the availability of NICE recommended therapies for some years [4,5] the treatment of patients with HCV in England remains sub-optimal. Successful treatment increases health and quality of life and reduces premature mortality from liver disease, which is a specific government target for improvement and public health outcome [10,11]. Improving access to hepatitis C treatment services will also help to reduce health inequalities as many of those infected belong to marginalised groups of society [12].

JOURNAL OF HEPATOLOGY

The Government's 2004 Hepatitis C Action Plan for England [13] called for 'high-quality services for the assessment and treatment of all patients with hepatitis C be co-ordinated and accessible across the country'. However, countrywide assessment of service provision has not been possible over recent years because national surveillance systems do not monitor referral and treatment. Consequently, progress towards achieving the provision required by the 2004 action plan is not easily assessed and it remains difficult to evaluate any impact on the future burden of hepatitis C. This study aims to provide a national estimate of the number of people who have received HCV treatment using a number of alternative data sources, and to assess the impact and associated costs of various treatment strategies on the future burden of HCV-related disease in England. Results from this work are intended to raise awareness of the existing level of treatment coverage in England, the consequent future burden of hepatitis C and the likely impact of increased treatment on this burden. This awareness is crucial to inform commissioning of treatment services and ensure that they are configured in a way that allows easy access to those groups that need them most.

Materials and methods

The analysis consists of three steps: (1) estimating numbers of patients treated in the period 2006–2011 via datasets relating to total volumes of drugs used for hepatitis C treatment; (2) applying a back-calculation approach to estimate the current disease-stage and age distribution of the infected population and progression probabilities within a health-state model; and (3) using the estimated model to predict future burden under different scenarios for the proportion of those with chronic infection treated each year.

Data on drugs used for treatment of hepatitis C

Three data sources representing volumes of drugs used to treat HCV were used to estimate the number of people treated annually for HCV.

(i) Ex-factory sales to NHS hospitals
The use of ex-factory sales data was negotiated with the drug companies who were sole suppliers of the components of anti-HCV combined therapy: (Roche: peginterferon alfa-2a Pegasys and the ribavirin Copegus; Schering Plough (now Merck Sharp & Dohme) peginterferon alfa-2b Viraferon-Peg and the ribavirin Rebetol). The companies provided data for the years 2006–2011 for hospitals and dispensing pharmacies in England.

(ii) Pharmex – National usage by primary buying groups
These data consist of NHS hospital-sector annual usage of the components of combined therapy by primary buying groups in England – largely equivalent to Regions. The estimates are derived from data collected via the DH Commercial Medicines Units' Pharmex system [14] (covering 97% of the constituent NHS Trusts).

(iii) IMS HEALTH Hospital Pharmacy Audit Index (HPAI)
IMS data on the amount of the components of anti-HCV combined therapy dispensed in 2006–2011 were used. These data were supplied via drug companies by arranging third party data sharing agreements. IMS collect information from 97% of English acute hospitals on all medicines dispensed in hospitals.

Data from all three sources were used to calculate the number of weeks of treatment in 2006–2011, based on recommended weekly doses of pegylated interferon for chronically infected patients. Data on ribavirin were also used for validation, although calculations require more assumptions due to weight-specific dosing and adjustment. The NICE template definitions for the length of treatment used by patients with HCV genotypes 1 and 4, or 2 and 3 [5], and the distribution of these genotypes in England [15] were used to calculate the average number of weeks' treatment required for each patient. Briefly, 55% of patients are assumed to have genotypes 1, 4, 5, or 6; of whom 46% discontinue early at 12 weeks, with the remainder receiving 48 weeks of treatment; those with genotypes 2 and 3 receive 24 weeks of treatment [5]. We assessed sensitivity to these assumptions using values of 37% and 55% discontinuations for genotypes 1, 4, 5, or 6; and 20% and 50% discontinuation at 12 weeks for genotypes 2 and 3. The number of weeks dispensed, sold or prescribed divided by the average number of weeks of treatment required was used to give estimates of the number of patients treated in 2006–2011, obtained by averaging estimates from the three different sources. Further details are available in Supplementary data, section "Calculation of the number of doses of pegylated interferon".

Back-calculation model

Analyses were based on previous work [2], which estimated the burden of HCV in England via **back-calculation**, using data on disease end points and information on progression rates [16]. A multistate model was constructed to represent the evolution of HCV infection through disease states: acute infection, infection clearance, mild chronic HCV, moderate chronic HCV, cirrhosis, decompensated cirrhosis (end-stage liver disease; ESLD), hepatocellular carcinoma (HCC), and death. Hospital episode statistics (HES) data on ESLD and HCC; and Office of National Statistics (ONS) data on HCC mortality were used as disease endpoints. Both datasets were grouped into 10-year age bands prior to analysis. The number of hospital episodes for ESLD (defined by ICD10 codes for ascites (R18), bleeding oesophageal varices (I850); hepato-renal syndrome (K767), hepatic encephalopathy or hepatic failure (K704, K720, K721, K729)) and HCC (ICD10 code C22.0) were available from HES for the period April 1995 to March 2009. Multiple episodes for the same individual within a year were identified and excluded using the unique HES ID number. Death entries with any mention or code for primary liver cancer or HCC (ICD9 155.0, ICD10 C22.0) and any mention or code for hepatitis C infection were included for the period 1996–2009; and the observed data were corrected for under-reporting within the model [2].

Information on the probabilities of progressing through the disease states was taken from the literature as in Sweeting *et al.* [2] and combined with the above data to derive estimates of the underlying incidence of infection and the number of individuals in each disease state over time. Moreover, an estimate of the overall adult anti-HCV prevalence was used to constrain the total number of infected individuals in 2005 [1]. Resulting estimates are then consistent with current estimates of the infected population size and observed data on ESLD, HCC, and HCC mortality. Further details are available in Supplementary data, section "back-calculation model".

Burden projection

The numbers of individuals in each health state in 2012 and progression probabilities estimated by the back-calculation model were used to generate future projections, based on the assumption that the progression probabilities remain the same over time. We also assumed continued incidence of 5000 infections (HCV antibody positive) per year, based on the back-calculation estimate for the period 2006–2010. This estimate is imprecise, but broadly consistent with evidence on the population size of injecting drug users [17,18], previous estimates of the proportion susceptible [1] and the force of infection applied to this population [19], from which the bulk of new infections arise. This pragmatic assumption leads to a relatively stable overall prevalence of chronic infections (in the absence of treatment) between 2010 and 2020 that then declines slowly by around 20% by 2040.

During each year, a proportion of those in chronic, moderate, and cirrhotic states are assumed to be treated; and may then achieve sustained viral response (SVR) with age, disease state, and genotype-specific probabilities estimated from an observational cohort of patients in clinical practice, which should broadly reflect the HCV-infected population in the UK [20]. These probabilities are based on intention to treat analysis, and hence discontinuation and adherence issues are assumed to be incorporated in the overall response rate. Briefly, those aged 40 with non-1 genotype have SVR probabilities of 0.82, 0.70, and 0.40 for mild, moderate, and cirrhosis states; while those with genotype 1 have probabilities of 0.57, 0.37, and 0.11. Those 10 years younger/older have probabilities of SVR around 0.05–0.10 higher/lower; and in the absence of information on probabilities in other age groups, we assumed younger/older groups to be the same as the youngest/oldest known group. Upon achieving SVR, patients in mild and moderate states are no longer at risk of progressing further and have comparable mortality to the general population; although higher rates were assessed in sensitivity analyses, with a five-fold increase in those aged 20–59. Those with compensated cirrhosis are assumed to still be at risk of further progression, but at a reduced rate [21]. Those failing to respond to treatment continue to progress through health states as before, and are not treated again. Progression through health states and treatment is shown in Fig. 1. We also assumed some of those with ESLD

Research Article

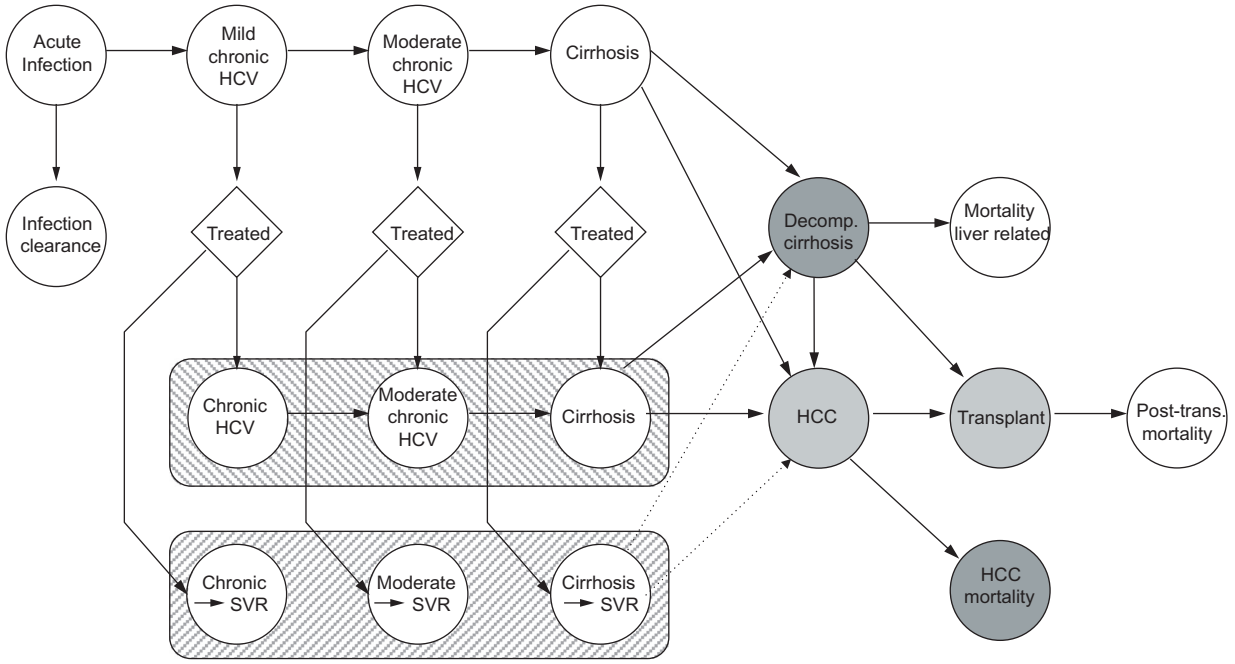

Fig. 1. Health-state model describing the natural history of hepatitis C, treatment states, followed by failure or sustained viral response, liver transplants, and death. Note that in all states death by natural causes may occur; this has not been shown for clarity. Shaded circles denote observed data (up to 2010). SVR, sustained viral response; HCC, hepatocellular carcinoma.

and HCC receive liver transplants, at a fixed rate of 2.5% and 10% per year respectively, based on national transplant data and current estimates of HCV burden [3]. Annual post-transplant survival probabilities for HCV patients were taken from Thuluvath *et al.* [22]. Further details are given in Supplementary data, section "back-calculation model".

Treatment scenarios

We based estimates of overall proportions treated annually on the three sources of pegylated interferon doses for 2006–2011, assuming the same level in 2012 as 2011; and approximately 11,200 treated during 2002–2005 [23], with the effect of treatment before this assumed to be negligible. As individuals are more likely to be diagnosed and treated as disease progresses, we assigned greater proportions treated in more advanced disease states, with 2%, 3%, and 6% of mild chronic HCV, moderate chronic HCV, and compensated cirrhosis patients treated annually for our baseline scenario, based on data from the Trent cohort [20]. Treatment then continues at 2012 levels, or is increased in alternative scenarios from 2013 onwards. The different scenarios are summarised in Table 1.

The potential impact of new and future treatments was also assessed. Recent studies on the direct acting antivirals (DAAs) Boceprevir [24,25] and Telaprevir [26] have indicated that SVR rates can be greatly improved in those with the more difficult to treat genotype 1 infection. In addition, many new drugs are in development or likely to be approved soon that show promise of delivering SVR rates close to 100% with interferon-free regimens regardless of genotype [27,27–29], although the efficacy in those with cirrhosis has not been well evaluated, and early reports indicate SVR rates may be lower [30]. We assume that new treatments will be gradually introduced such that the average probability of SVR in a treated patient will increase steadily from those reported in Thomson [20] to an optimum level in 2018, with 90% SVR in those with mild or moderate chronic HCV and 60% in those with compensated cirrhosis. We assessed the impact of such treatments under scenarios 3–7 (Table 1).

The impact of different scenarios on the numbers of individuals in each health state was assessed, focussing on ESLD/HCC incidence over the next 30 years. We examined the estimated number of cases under each scenario, and differences in comparison with the base case (either current levels, or no treatment). Costs associated with each state [31] were applied to the resulting numbers in order to determine the additional cost of implementing different treatment scenarios, and the cost per case of ESLD/HCC averted. The latter is an incremental comparison according to the standard formula:

$$\text{ICER} = (C_2 - C_1)/(E_1 - E_2)$$

where C_i and E_i are the cost and number of events respectively under scenario i, and scenario 2 is being compared to the base case scenario 1. Results are presented in UK pounds sterling. Healthcare costs were adjusted according to the hospital community health services pay and prices index [32], and we examined the impact of discounting events and costs according to NICE guidelines [33]. We examine the costs of standard treatment with pegylated interferon and ribavirin only, given the rapidly changing landscape of hepatitis C treatment [29] and uncertainty of costs for new drugs. Further details on the burden model and assumed costs are given in Supplementary data, section "costs".

The back-calculation model was implemented in a Bayesian framework using WinBUGS [34]. Predictions are a function of the estimated parameters combined with scenario inputs, and are therefore obtained via a process akin to probabilistic simulation. Resulting quantities of interest reflect uncertainty in the information used, which is expressed via credible intervals (CrI), the Bayesian equivalent of a 95% confidence interval. To assess the robustness of our conclusions and determine factors driving the results, we varied the parameters in the model in sensitivity analyses (one factor at a time), including different rates of SVR, disease progression and background mortality; different proportions treated in each disease state; and cost of drugs.

Results

Trends in treatment levels

The estimated number of HCV-positive patients receiving combination therapy based on pegylated interferon sold, purchased, and dispensed 2006–2011 gave similar estimates (Fig. 2). In 2006, sufficient pegylated interferon was sold, purchased or dispensed to treat an average of 3234 individuals. Treatment levels rose annually from 3234 in 2006 to 5316 in 2010, but the annual increase slowed over time and decreased between 2010 and 2011 (Fig. 2).

Sensitivity analyses for a discontinuation rates in genotype 1, 4, 5, or 6 of 37% and 55% resulted in a ± 6% difference in estimated

Table 1. Treatment scenarios examined in the burden projection model.

Scenario	Description
1. No treatment	Hypothetical projection of future burden in the absence of past and future treatment
2. Past treatment	Hypothetical projection of future burden in the absence of future treatment
3. Current (baseline scenario)	Treatment levels continue at 2%, 3% and 6% for mild, moderate and cirrhosis
4. Increase 1 (50%)	Treatment rates double over the next 10 years, resulting in a 50% increase in numbers treated annually in 2023.
5. Increase 2 (100%)	Treatment rates triple over the next 10 years, resulting in a 100% increase in numbers treated annually in 2023.
6. Gradual complete coverage	Treatment rates increase as above (5), then continue to rise from 2023 until 100% coverage is achieved in 2043.
7. Rapid complete coverage	Treatment rates rise rapidly from 2013, with up to 30,000 per year treated and 100% coverage achieved in 15 years.

Note: all increases in treatment over time are via a linear increase in the annual proportion treated.

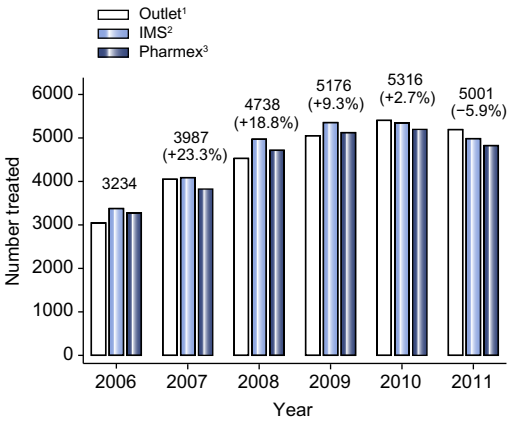

Fig. 2. Numbers of HCV-positive patients receiving combination therapy based on pegylated interferon sold, purchased and dispensed 2006–2011. Average numbers from the three data sources and percentage annual change in parentheses. Sources: [1]Outlet Data on sales of pegylated interferon supplied by Roche and Merck, Sharpe & Dohme Ltd, 2006–2011. [2]IMS SCM Data on pegylated interferon dispensed, Published Feb 2012, showing units to hospital outlets, 2006–2011. [3]Pharmex Data, on interferon purchased, 2006–2011, supplied by the Department of Health's Commercial Medicines Unit.

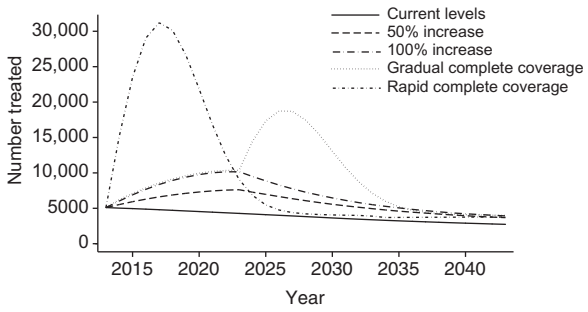

Fig. 3. Annual numbers treated under different scenarios. Current levels: approximately 3% of previously untreated individuals are treated annually; 50% and 100% increase steadily increases annual treatment rates such that numbers are 50% and 100% higher by 2023; gradual and rapid complete coverage increases treatment such that all previously untreated individuals are given treatment within 30 and 15 years respectively.

numbers. If 20% of those with genotypes 2 and 3 also discontinue at 12 weeks, estimated numbers treated are 5% higher; if this rate were 50%, numbers treated are 13% higher.

Future burden of HCV and impact of treatment

Fig. 3 shows the numbers treated under current levels, and for the four scenarios of increased treatment (4–7). Under current treatment levels the number treated each year decreases over time as the pool of untreated individuals declines, as the assumed level of incidence is not high enough to maintain current prevalence. Under the two scenarios for a gradual increase over the next 10 years, numbers treated are assumed to rise from 5000 per year to around 7500 and 10,000 respectively by 2023, before stabilising at a fixed proportion treated; again, numbers treated fall off as the pool of untreated individuals decreases. Scenario 6 assumes that over 30,000 individuals are treated in 2014, with the proportion treated annually remaining high. The pool of untreated individuals decreases quickly however, so that the very high numbers treated are not sustained for long.

Fig. 4 shows the predicted incidence of HCV-related ESLD and HCC over the next 30 years according to different treatment strategies. In the absence of any treatment, annual incidence would be predicted to rise to a peak of 2290 (95% CrI 2000–2750) in 2035. Treatment between 2006 and 2012 was predicted to have some impact on future burden (predicted incidence: 2080 (95% CrI 1820–2520) in 2035), but must continue in order to make a significant impact. By 2035, annual incidence of HCV-related ESLD/HCC under current treatment levels was predicted to be 640 (95% CrI 550–760) cases fewer than without treatment. Increasing treatment from current levels was predicted to reduce incidence by a further 180 or 290 cases per year by 2035 with a 50% and 100% increase respectively. However, the gains made by increasing treatment are relatively long-term unless very large numbers are treated immediately; increases in treatment were predicted to halt the rise in incidence more quickly, but only by rapidly increasing to nearly complete coverage can the predicted rise in incidence of HCV-related ESLD and HCC be halted in the near future.

Introduction of more effective treatments was predicted to have a major impact on future burden, with treatment at current levels preventing approximately the same number of incident ESLD/HCC as a 100% increase in standard treatment; and doubling treatment levels with the more effective treatments having more impact than rapid complete coverage of standard

Research Article

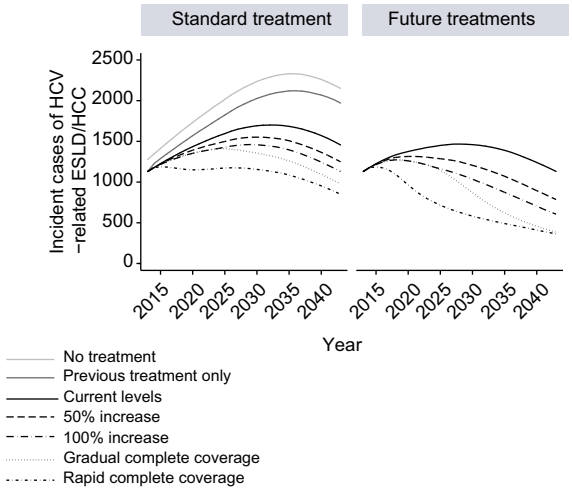

Fig. 4. Predicted annual incidence of HCV-related end-stage liver disease and hepatocellular carcinoma (ESLD/HCC) over the next 30 years according to the implementation of different treatment scenarios. Left panel shows different levels of treatment using current regimen; right panel using future treatments with increased response rates. Current levels: approximately 3% of previously untreated individuals are treated annually; 50% and 100% increase steadily increases annual treatment rates such that numbers are 50% and 100% higher by 2023; gradual and rapid complete coverage increases treatment such that all previously untreated individuals are given treatment within 30 and 15 years respectively.

treatment. Despite these improvements, it is some time before incidence of ESLD/HCC is reduced by a substantial level, even when combined with a large increase in coverage: the gradual and rapid complete coverage scenarios with more effective treatment predicted annual incidence of 620 (95% CrI 540–760) and 490 (95% CrI 430–580) respectively in 2035.

Cost of treatment

The total cost of maintaining current treatment levels (3%) with pegylated interferon and ribavirin (or a regimen of similar cost) over the next 30 years was estimated to be £910 million (95% CrI 730–1210) greater than no treatment; this being the difference in total healthcare and treatment costs between the two scenarios. Increasing treatment to 50% and 100% more patients treated within 10 years results in an additional total cost of £460 million (95% CrI 380–600) and £740 million (95% CrI 610–970) respectively over the next 30 years. The cost per incident ESLD/HCC case averted was estimated to be £128,000 (95% CrI 110,000–152,000) for a 50% increase; and very similar for a 100% increase and rapid complete coverage at £126,000 and £111,000 respectively. It should be kept in mind that the results above assume the same SVR rates and costs over time and do no incorporate discounting. Assuming a discount rate of 3.5% increases the cost per case averted to £169,000, reflecting that treatment costs tend to be incurred in the short-term whereas the reduction in ESLD/HCC occurs later in time. With a discount rate of 1.5%, which NICE suggests when health benefits may be sustained over a long period, the cost per case averted was £143,000.

The total additional cost for implementing rapid complete coverage was estimated at £1460 million (95% CrI 1170–1890) over the next 30 years. These are substantial costs; however, the total healthcare cost of the HCV-infected population over the next 30 years under current treatment levels was estimated to be £4680 million (95% CrI 3770–5900). Therefore, although treatment costs are substantial, they are still relatively small compared to the total cost of disease burden.

Sensitivity analyses

We assessed the sensitivity of our results to changes in parameter values and assumptions, using 100% increase *vs.* current treatment for comparisons. Change in progression rates had a large effect: with 50% faster progression between each state the predicted disease burden is nearly doubled, but treatment then has more impact as a greater number of ESLD/HCC cases are prevented, with a cost per case averted of £66,000 compared to £126,000 for the base case. Conversely, 50% slower progression nearly halves the predicted burden, and the cost per case averted is therefore far higher at £254,000. Changes in SVR rates (assuming the same cost of treatment) have relatively little impact on predicted disease burden, given the relatively low levels of treatment for these scenarios, but gave a cost per case averted of £105,000 if SVR rates are 50% higher (an odds ratio of 1.5) and £153,000 if SVR rates are 50% lower. Higher background mortality (five times higher in those aged 20–59) reduces the prediction of future burden, as more people die from other causes before reaching ESLD/HCC states, reducing the peak burden to 1100 cases per year. The cost per case averted therefore increases to £163,000 under this scenario. As there is a delay between treatment and prevention of ESLD/HCC, using a longer time window also reduces the cost per case averted, at £45,000 over a 70 year window, with a greater proportion of prevented cases post-2043. More details of sensitivity analyses are given in Supplementary data, section "sensitivity analyses".

Discussion

Principal findings

Supply, dispensing and purchasing data suggest that around 28,000 patients were treated from 2006 to 2011; approximately 17% of those estimated to have chronic hepatitis C infection in England in 2005 [1]. The number treated increased from 2006 to 2010, but has not increased subsequently. Treatment for HCV with pegylated interferon and ribavirin has been introduced relatively recently; so far, treatment levels have been too low (and end points too distant) to assess the impact on disease burden, as has been done, for example, for HIV; and government action plans were only issued in 2004 [35]. We therefore assessed the potential impact of treatment via projections of future burden, based on knowledge of disease progression and response to treatment. These analyses provide a strong argument for increasing levels of treatment, ideally as soon as possible.

Strengths and weaknesses

The use of dispensing and purchasing data to estimate trends in numbers treated has some limitations. Pegylated interferon monotherapy may be prescribed to a small number of HCV positive patients who have ribavirin intolerance. Pegylated interferon alfa-2a is also prescribed for patients with chronic hepatitis B

infection; however, this is likely to account for only a small number of patients: the NICE costing template for hepatitis B used estimates of 154 patients treated with pegylated interferon alfa-2a in 2006 [36]. Estimates based on ribavirin data gave slightly lower numbers, but agreed well with the patterns obtained from the pegylated interferon data. Neither Pharmex nor IMS data cover all hospitals in England, although only two of the nine hospitals that do not contribute data to IMS or Pharmex were listed as potential treating centres for HCV. Finally, average treatment lengths are based on those reported by NICE [5] and in the absence of further information we do not know how accurate these are in the general population. Early stopping in genotype 1 patients are accounted for in the NICE template, but all of those with genotypes 2 and 3 are assumed to complete a 24 week course. However, sensitivity analyses assuming as much as 50% with genotypes 2 and 3 and 55% of other genotypes stopping at 12 weeks do not change our estimates by more than 20% (Supplementary data, section "Calculation of the number of doses of pegylated interferon"). Our results should therefore reflect broad trends and the general level of current treatment.

The projection of future burden in England is based on the best evidence currently available. The back-calculation model uses estimates of disease progression from the literature as prior information, and this information is combined with the observed data on disease endpoints and current best estimates of overall disease prevalence. Transition rates and intervention effects for treatment were obtained from population-based studies in the UK, and we have used age-specific transition rates to address heterogeneity, as recommended in Siebert *et al.* [37]. Therefore the model produces results that are consistent with the overall picture of the natural history and disease burden of hepatitis C in England today. However, it must be borne in mind that our results rest on the assumption that the model structure is correct and the data we have used are not subject to systematic bias; therefore the relatively narrow credible intervals may give an over-optimistic impression of confidence in these results. In terms of validation, the model fits the national data well and, for instance, resulting progression probabilities are similar to those of the UK cohort studies upon which they are based (the model is **internally consistent**). However the model has not been formally **externally** validated. As all relevant national data have been used to fit the model, any external validation would need to be carried out using data from other countries or settings. This is outside the scope of this work, although we are actively looking for such opportunities. However, an informal assessment shows that our estimated progression probabilities are comparable to studies in France and the US [38,39], with a 20-year probability of progressing to cirrhosis of 14% in 40–49 year olds. Some studies have reported higher rates [40]; although these vary greatly depending on setting [41], alcohol use [38], and duration of infection [41] and with an apparent difference in rates by country [23]. These issues are further discussed in Supplementary data, section "back-calculation model".

Projections have been derived under some simplifying assumptions. Incidence has been assumed constant, which could change substantially in the future, particularly if successful treatment results in decreased transmission of HCV [42]. However, as the main focus is on ESLD/HCC occurring over the next 30 years, changes in incidence will have comparatively little impact on disease endpoints within this time frame. The model also does not include re-infection, leading to an over-estimate of the number remaining clear of infection in this cohort over time; although conversely, the possibility of re-treating those who fail to achieve SVR has also not been considered. Further assumptions are that the progression probabilities will not change over time. This could potentially impact on future burden: sensitivity analyses indicate that the predicted burden is highly dependent on progression probabilities. Another area of uncertainty is mortality from other causes; which, if higher, would result in less HCV-related morbidity. It was not possible to account for differing progression rates due to alcohol and other factors: this would require better information from cohort studies and remains an area of future research.

Our study contains elements of cost-effectiveness analysis, but we have not applied discounting in our main results, where future benefits (and costs) are down-weighted. This is because our main aim is to enumerate absolute costs and increases using the same type of treatment, rather than comparing "competing" strategies or technologies. Discounting results in a greater cost per ESLD/HCC case averted; this is because disease progression is typically slow; and reductions in ESLD/HCC from increasing treatment is a long-term goal.

Finally, we have not considered the additional costs of increasing treatment uptake in terms of increased case finding, health promotion campaigns, and improved infrastructure that might be required. These costs may be substantial to achieve very high levels of coverage; although improved treatment options, especially easy-to-tolerate interferon-free regimes, seem likely to naturally result in increased uptake.

Implications for clinicians and policymakers

Supply, dispensing, and purchasing data suggest that treatment of chronically HCV-infected individuals rose by 20% per year from 2006 to 2008, but has declined recently. Between 2006 and 2011 an estimated total of approximately 28,000 individuals have been treated. These low treatment levels indicate that many individuals are failing to access appropriate management country-wide.

If the future burden of HCV-related disease is to be averted, significant increases in treatment need to be achieved, and NICE have recently issued guidance to ensure that more people at increased risk of hepatitis C (and B) infection are offered testing and treatment services [43]. While reorganisation of the NHS in England poses a challenge to hepatitis C provision, particularly for those marginalised groups of society who are most affected by the virus, it also provides opportunities for better co-ordination of services; the development of integrated services that reach into communities – whether based in primary care, drug services, prisons or elsewhere – will be key for increasing access to HCV treatment.

There are a number of new drugs under development with the likely prospect of interferon-free regimes in the near future [27]. Achieving high cure rates has so far been hampered by treatment regimes that are difficult to tolerate and have low SVR rates for genotype 1 patients and those with advanced fibrosis. Although DAAs offer an improvement in SVR rates, they have been associated with higher rates of adverse events [44] and are costly [45]. The introduction of safe, orally administered treatment that is effective across genotypes could radically change the picture of hepatitis C treatment today, as such drugs could be rolled out in the community and achieve widespread coverage. Despite the strong possibility that such treatments are on the way, it

remains to be seen whether the costs of these new treatments will be acceptable. Exact costs of new drugs such as Sofosbuvir are not yet available, but are likely to be high [46]. Given the costs for treating large numbers of people even with standard treatment, the total costs for new drugs will be significant. However, this must be offset against savings in other healthcare costs, such as the management of end stage liver disease and liver transplant. The landscape of hepatitis C treatment is changing rapidly and it seems an era of vastly improved treatment is on the way. In the mean time however, disease burden is rising and there remains a pressing need for infected patients to be treated as soon as possible.

Final remarks

Monitoring treatment and treatment outcomes in patients with HCV infection must be an ongoing process, especially with the advent of new therapies [7,8,28]. This requires the availability of regular and reliable estimates of the number living with HCV infection and those who are receiving treatment. As such, there is an urgent need for service providers to supply accurate information on the numbers of individuals referred and treated, as well as on the outcomes of treatment. These can then be used with the type of models described here to estimate future disease burden, which is essential for local planning of treatment and care services. If the increases in cirrhosis and deaths from HCV-related disease that have been predicted in England are to be averted, commissioners will need to consider expanding provision of treatment in non-traditional settings, including primary care, drug treatment settings and prisons. It is vital to make treatment more accessible for those groups who need it most and address the health inequalities that result from excess premature deaths from HCV-related liver disease in marginalised populations.

Financial support

This work was supported by the Department of Health (Grant number 408476). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Acknowledgments

We would like to thank the following organisations for the provision of data: Hospital Episode Statistics (Copyright © 2012, re-used with the permission of The Health and Social Care Information Centre, all rights reserved); the Office for National Statistics (ONS carried out the original collection and collation of the data but bears no responsibility for their future analysis or interpretation); Roche; Merck, Sharp & Dohme Ltd; IMS Health; the Department of Health's Commercial Medicines Unit. We also thank Michael Sweeting, who developed the original burden model upon which this work is based; and Charles Gore, Sylvie Deuffic-Burban, Jeremy Goldhaber-Fiebert and two anonymous referees, who all provided valuable comments on this manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2014.05.008.

References

[1] Harris RJ, Ramsay M, Hope VD, Brant L, Hickman M, Foster GR, et al. Hepatitis C prevalence in England remains low and varies by ethnicity: an updated evidence synthesis. Eur J Public Health 2012;22:187–192.
[2] Sweeting MJ, De Angelis D, Brant LJ, Harris HE, Mann AG, Ramsay ME. The burden of hepatitis C in England. J Viral Hepat 2007;14:570–576.
[3] Harris HE, Ramsay ME, editors. Hepatitis C in the UK 2012 Report. London: Health Protection Agency, Colindale; 2012.
[4] National Institute for Health and Clinical Excellence. Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C 75; 2004. Technology Appraisal.
[5] National Institute for Health and Clinical Excellence. Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C 106. NICE technology appraisal guidance; 2006.
[6] National Institute for Health and Clinical Excellence. Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C 200. NICE technology appraisal guidance; 2010.
[7] National Institute for Health and Clinical Excellence. Boceprevir for the treatment of genotype 1 chronic hepatitis C 253. NICE technology appraisal guidance; 2012.
[8] National Institute for Health and Clinical Excellence. Telaprevir for the treatment of genotype 1 chronic hepatitis C 252. NICE technology appraisal guidance; 2012.
[9] Parkes J, Roderick P, Bennett-Lloyd B, Rosenberg W. Variation in hepatitis C services may lead to inequity of health-care provision: a survey of the organisation and delivery of services in the United Kingdom. BMC Public Health 2006;6:3.
[10] Healthy lives, healthy people: improving outcomes and supporting transparency. London: Department of Health; 2012.
[11] Department of Health. The NHS outcomes framework 2013–14. London: Department of Health; 2012.
[12] Health Protection Agency, Harris HE, Ramsay ME, editors. Hepatitis C in the UK 2012 report. London: Health Protection Agency, Colindale; 2012.
[13] Department of Health. Hepatitis C action plan for England. London: Department of Health; 2004.
[14] Department of Health. Commercial medicines unit. http://cmu.dh.gov.uk/; 2014 [accessed 28.2.14].
[15] Harris HE, Ramsay ME, editors. Hepatitis C in the UK 2009. London: Health Protection Agency Centre for Infections; 2009.
[16] Brookmeyer R, Gail MH. Minimum size of the acquired immunodeficiency syndrome (AIDS) epidemic in the United States. Lancet 1986;2:1320–1322.
[17] King R, Bird SM, Hay G, Hutchinson SJ. Estimating Prevalence of Injecting Drug Users and Associated Death Rates in England Using Regional Data and Incorporating Prior Information; 2012.
[18] Hay G, Gannon M, MacDougall J, Eastwood C, Williams K, Millar T. Capture–recapture and anchored prevalence estimation of injecting drug users in England: national and regional estimates. Stat Methods Med Res 2009;18:323–339.
[19] Sutton AJ, Gay NJ, Edmunds WJ, Hope VD, Gill ON, Hickman M. Modelling the force of infection for hepatitis B and hepatitis C in injecting drug users in England and Wales. BMC Infect Dis 2006;6:93.
[20] Thomson BJ, Kwong G, Ratib S, Sweeting M, Ryder SD, De Angelis D, et al. Response rates to combination therapy for chronic HCV infection in a clinical setting and derivation of probability tables for individual patient management. J Viral Hepat 2008;15:271–278.
[21] Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol 2010;8:280–288.

[22] Thuluvath PJ, Krok KL, Segev DL, Yoo HY. Trends in post-liver transplant survival in patients with hepatitis C between 1991 and 2001 in the United States. Liver Transpl 2007;13:719–724.
[23] Deuffic-Burban S, Deltenre P, Buti M, Stroffolini T, Parkes J, Muhlberger N, et al. Predicted effects of treatment for HCV infection vary among European countries. Gastroenterology 2012;143:974–985.
[24] Kwo PY, Lawitz EJ, McCone J, Schiff ER, Vierling JM, Pound D, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. Lancet 2010;376:705–716.
[25] Poordad F, McCone Jr J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1195–1206.
[26] Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;364:2405–2416.
[27] Stedman CA. Current prospects for interferon-free treatment of hepatitis C in 2012. J Gastroenterol Hepatol 2013;28:1440–1746.
[28] Lok AS, Gardiner DF, Hezode C. Sustained virologic response in chronic HCV genotype (GT) 1-infected null responders with combination of daclatasvir (DCV; NS5A inhibitor and asunaprevir (ASV; NS3 inhibitor) with or without peginterferon alfa-2a/ribavirin (PEG/RBV), 12 Nov 9; Boston; 2012.
[29] American Association for the Study of Liver Diseases and Infectious Diseases Society for America. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org/full-report-view; 2014 [accessed 20.2.14].
[30] Soriano V, Gane E, Angus P, Stickel F, Bronowicki J-P, Roberts S, et al. The efficacy and safety of the interferon-free combination of BI201335 and BI207127 in genotype 1 HCV patients with cirrhosis – interim analysis from SOUND-C2. Barcelona, Spain: The International Liver Congress 2012; 2012.
[31] Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. Interferon alpha (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. Health Technol Assess 2007;11:1–205, iii.
[32] Department of Health. Hospital and Community Health Services (HCHS) pay and price inflation; 2010.
[33] National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. NICE public health guidance; 2013.
[34] Spiegelhalter D, Thomas A, Best N, Lunn D. WinBUGS Version 1.4 User Manual. Cambridge: MRC Biostatistics Unit; 2003.
[35] Aalen OO, Farewell VT, De Angelis D, Day NE, Gill ON. New therapy explains the fall in AIDS incidence with a substantial rise in number of persons on treatment expected. AIDS 1999;13:103–108.
[36] National Institute for Health and Clinical Excellence. Costing template and costing report. Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B 96. NICE technology appraisal; 2006.
[37] Siebert U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ, et al. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-3. Med Decis Making 2012;32:690–700.
[38] Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology 2008;48:418–431.
[39] Deuffic-Burban S, Deltenre P, Louvet A, Canva V, Dharancy S, Hollebecque A, et al. Impact of viral eradication on mortality related to hepatitis C: a modeling approach in France. J Hepatol 2008;49:175–183.
[40] Salomon JA, Weinstein MC, Hammitt JK, Goldie SJ. Empirically calibrated model of hepatitis C virus infection in the United States. Am J Epidemiol 2002;156:761–773.
[41] Sweeting MJ, De Angelis D, Neal KR, Ramsay ME, Irving WL, Wright M, et al. Estimated progression rates in three United Kingdom hepatitis C cohorts differed according to method of recruitment. J Clin Epidemiol 2006;59:144–152.
[42] Martin NK, Vickerman P, Miners A, Foster GR, Hutchinson SJ, Goldberg DJ, et al. Cost-effectiveness of hepatitis C virus antiviral treatment for injection drug user populations. Hepatology 2012;55:49–57.
[43] National Institute for Health and Clinical Excellence. Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection 43. NICE public health guidance; 2012.
[44] Hezode C, Dorival C, Zoulim F, Poynard T, Mathurin P, Pol S et al. Safety of Telaprevir or Boceprevir in combination with Peginterferon alfa/Ribavirin, in cirrhotic non responders. First results of the French early access program (ANRS CO20-CUPIC). In: 47th Meeting of the European Association for the Study of the Liver (EASL), Barcelona; 2012.
[45] Liu S, Cipriano LE, Holodniy M, Owens DK, Goldhaber-Fiebert JD. New protease inhibitors for the treatment of chronic hepatitis C: a cost-effectiveness analysis. Ann Intern Med 2012;156:279–290.
[46] New York Times; F.D.A. Approves pill to treat hepatitis C. http://www.nytimes.com/2013/12/07/business/fda-approves-pill-to-treat-hepatitis-c.html; 2014 [accessed 19.1.14].